legislative update

In February, our board of directors met in Washington, DC, for our quarterly board meeting along with two full days of advocating for our legislative priorities in the Senate, House, and with the U.S. Food and Drug Administration (FDA). This year, we visited 41 one of our senators and representatives to discuss three key priorities, which include:

- Orphan Drug Tax Credit
- Patient Access to Treatment Act H.R. 460
- Out of Network Classification concerns with the Affordable Care Act

National MPS Society board of directors and staff at FDA

In addition to meeting with our legislators, the Society's full board of directors had a meeting with the FDA's key leadership to discuss how we can partner to speed research and development of life-saving drugs to our MPS and related disease patients. It was a robust conversation that covered topics of risk versus benefit, patient/caregiver treatment tolerance levels, alarming trends of offshoring of early phase enzyme replacement therapy clinical trials for MPS, and efficient development of gene therapies. The FDA was responsive to our concerns and provided valuable feedback about how the FDA is aware of and is addressing each of these topics. Meeting with the key leaders is a huge step forward in building the bridge between the experience and knowledge of MPS patients with the rigorous demands of regulating and approving safe and effective trials for life-saving treatments.

Annabelle Bozarth (MPS IVA), participant in ERT pivotal trial

Another exciting accomplishment came from our advocacy as an MPS community and rare disease group. On Feb. 14, BioMarin Pharmaceutical, Inc. and the FDA announced the approval of a Biologics License Application (BLA) for a new biological product, called Vimizim™, for patients with MPS IVA. The approval of Vimizim not only marks the first FDA-approved product for Morquio A syndrome, but also the first time a company has secured a Rare Pediatric Disease Priority Review Voucher. This voucher was an incentive piece of legislation, also known as the Creating Hope Act, which was included in Section 908 of the 2012 FDA Safety and Innovation Act. We, as a society, advocated for this voucher program to be included and we are the first rare disease group to see this voucher acquired for an approval of a BLA to benefit MPS IVA. The voucher has potential to lead more investment in rare disease drug research and development.

In conclusion of our recent successful advocacy milestones, I want to invite all our members to engage in the conversation. Your voice is powerful as it comes from a unique perspective to provide context and passion. Our advocacy efforts are only as strong as our Society members stay engaged with their legislators and our government regulators. The MPS and rare disease communities have made great strides over the last few years in research, development, governmental regulations and legislative incentive building, and we are gaining momentum. Join us to keep the momentum accelerating!

Stephanie Bozarth, MSW
Chair, Committee on Federal Legislation
stephanie.bozarth@mpssociety.org

CALL TO ACTION!

Current Legislative Priorities and Action Items:

• Ask your Congressman to Join the Rare Disease Caucus
With the caucus now introduced in the 113th Congress, we need your help to drive membership. The caucus will help to further educate our legislators about the special needs of our MPS community and other rare diseases communities with similar issues. This is where we start our search for advocacy champions that can greatly influence legislation important to us. You will be able to determine if your congressman is in the caucus at **www.rarediseaseadvocates.org**.

• Orphan Drug Tax Credit (ODTC)
The ODTC was enacted in 1983 as a mechanism to incentivize the development of medications and treatments for rare diseases. In the decade before the ODTC, only 10 medicines were developed by industry for rare diseases. Since 1983, more than 2,700 potential treatments have entered the research pipeline as orphan drugs and more than 300 have been approved by the FDA. Despite this progress, there are approximately 7,000 rare diseases affecting about 30 million people in the United States. Most of these diseases have no cures or treatments.

• The Patients' Access to Treatment Act
This bipartisan piece of legislation limits exorbitant out-of-pocket costs for individuals requiring treatment with "specialty drugs." When medications become too expensive, many patients cut doses, skip doses or forego the medication altogether. The lives of children and families living with MPS and related diseases depend on medications that can fall into these specialty tiers. The legislation currently is in the House of Representative's Energy and Commerce Health Subcommittee.

Traditionally, commercial health insurers charge fixed co-pays for different tiers of prescription medications, such as generics (Tier I), name brands (Tier II) and formulary brand medications (Tier III). Co-pays increase as you move up the three tiers. Some commercial health insurers are now moving vital medications (mostly biologics for which there are no generic equivalents) into what are called "specialty tiers." Rather than charging a set co-pay to the patient, these tiers utilize a high patient cost-sharing method in which the patients pay a percentage of the actual cost of the drugs—from 25 percent to 33 percent or more. This can mean hundreds or even thousands of dollars per month for a single medication, rendering the medication unaffordable and impossible to utilize. For children and adults living with MPS diseases, many of the medications needed to stay alive fall into what would be considered specialty tiers.

• Out-of-Network Classifications
As the Affordable Care Act is implemented, it is essential that patients with rare diseases aren't hurt by out-of-network classifications. Provider networks must be broad enough that patients can afford to see the specialists they need without exorbitant co-pays and deductibles. Patients with MPS and related diseases require a myriad of specialized care in order to survive. In many cases, the types of specialists required are few and far between, which means that patients and families need to travel a distance to receive such specialized care. This spring, the Rare Disease Caucus will be hosting a briefing on this issue.

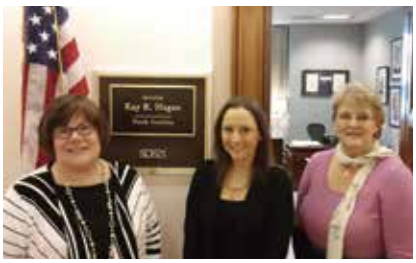
Legislative Committee:

Stephanie Bozarth, *chair*
Amy Barkley
Jeff Bardsley
Austin Bozarth
Dawn Checrallah
Lydia Edgal
Steve Holland
Terri Klein
MaryEllen Pendleton
Laurie Turner
Kim Whitecotton
Roy Zeighami
Barbara Wedehase

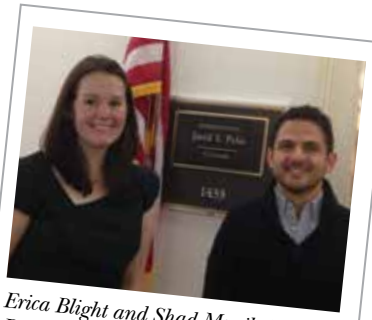
Advocacy 2014 Snapshots

Angela and Luis Guajardo with Ed Hill (middle) from Rep. Hinojosa's (D-TX) office

Carrie Dunn outside Sen. Booker's (D-NJ) office



Elizabeth Farrar, health aid to Sen. Hagan (D-NC), center, with Barbara Wedehase and Terri Klein



Erica Blight and Shad Murib from Rep. Jared Polis' (D-CO) office

Gordon Wingate, Tom Gniazdowski and Congressional Staffer Adam Scheidler from Rep. Steve Chabot's (R-OH) office

Sen. Stabenow (D-MI) with Austin Noll, Terri Klein and Kim Whitecotton

Amber Mongan, Justin Smith, MD, from the office of Sen. Ron Wyden (D-OR) and Stephanie Bozath

Steve Holland, Gordon Wingate, Sen. Ted Cruz (R-TX), Angela Guajardo and Luis Guajardo

Jonny Lee Miller, Luis Guajardo and Jill Wood at Rare Disease Caucus

Sen. Susan Collins (R-ME) with Laurie Turner

Steve Holland, Gordon Wingate, Sen. John Cornyn (R-TX), Angela Guajardo and Luis Guajardo

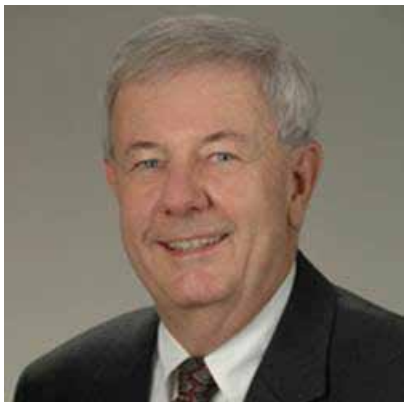
New Hope for Rare Disease Research and Treatments

by *Stephanie Fischer*

Dr. Richard Moscicki, Deputy Center director for Science Operations at the Center for Drug Evaluation and Research at the FDA, noted in his remarks at the FDA public workshop on Complex Issues in Developing Drug and Biological Products for Rare Diseases that more than a third of the novel drugs approved in CY13 treat rare disease. With 450 therapies in the pipeline, as shown in PhRMA's report on Medicines in Development for Rare Diseases, we are optimistic that this trend will continue.

One of the themes of the FDA workshop was the need for closer collaboration between the many stakeholders in the development of therapies for rare disease. Together, the biopharmaceutical industry, academia, government (particularly the FDA and National Institutes of Health) and patient advocacy organizations can make more progress in the quest for new treatments.

Following is a perspective on how we can address those complex issues in developing therapies for rare diseases, together, from Dr. Stephen Groft, director of the Office of Rare Diseases Research of the National Center for Advancing Translational Sciences at the National Institutes of Health (NIH). Last year, Dr. Groft received the Henri Termeer Lifetime Achievement Award from Global Genes for his 30-year commitment to rare disease research.



Dr. Stephen Groft

Growing up in the 1950s, I had friends and neighbors who were stricken with uncommon diseases with few or no effective treatments readily available. Cystic fibrosis, leukemia, brain tumors, Marfan syndrome, muscular dystrophy, cerebral palsy, polio, Multiple Sclerosis and Parkinson's disease were just some that I witnessed first-hand.

As I embarked on what would be a lifetime of commitment to advancing research on the approximately 6,500 rare diseases and conditions affecting millions of people, there still were relatively few therapeutics on the market. Recognizing the need for a strong patient advocacy voice led to the formation of what is now known as the National Organization for Rare Disorders (NORD). Individual organizations instrumental in passing the Orphan Drug Act of 1983 into law were responsible for the establishment of NORD. The Act, which provides for a number of incentives to expand research into developing new preventions, treatments and cures for rare diseases, has helped lead to more than 450 product approvals and treatments in the past 30 years.

While there has been amazing progress, the road ahead is still at times daunting as we strive to find better, quicker and less expensive methods to translate research discoveries into new interventions that meet safety and efficacy requirements. The encouraging news is that the rare disease community appears stronger than ever, and there has been no better time in history to build on existing momentum and resources. For example, the number of public-private partnerships continues to increase as new business models for rare disease drug development surface. Collaborative opportunities have expanded to include representation not only from academia and patient advocacy groups, but also from the pharmaceutical,

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>> biotechnology and diagnostic industries; philanthropic foundations; and research and regulatory government agencies.

Many NIH Institutes and Centers (ICs), including the National Center for Advancing Translational Sciences (NCATS), are deeply committed to fostering the collaborative efforts of multidisciplinary research teams and new approaches to drug discovery and development for rare diseases. The study of rare diseases enables NCATS to both address enormous unmet medical needs and can lead to an understanding of more common diseases. Through NCATS' Therapeutics for Rare and Neglected Diseases (TRND) program, researchers have the opportunity to work with TRND experts and use NCATS pre-clinical scientific capabilities and services in efforts to move promising small molecules and biologics into clinical testing. Another valuable resource for those who have hit roadblocks and need additional expertise is the Bridging Interventional Development Gaps program, which provides eligible scientists with access to contractor services, such as toxicology studies, for pre-clinical therapeutic development.

In addition, NCATS' Office of Rare Diseases Research co-funds some awards for the NIH Bench-to-Bedside program, which helps to address barriers in the translational research process, such as the traditional silos between basic and clinical researchers in biomedical research. While previously NIH's ICs funded research on individual rare diseases in their respective disease-type or organ domains, the Rare Diseases Clinical Research Network helps support broader and collaborative clinical trials and information sharing. Through these and similar initiatives, the rare disease community collectively now has the ability to attract a large number of research investigators with a particular interest in rare diseases.

Finally, we also now better understand how to conduct the most effective rare disease clinical trials, and I remain grateful that so many patients continue to be willing partners in these studies. The community's dedication and commitment, combined with the promises of gene therapy, regenerative medicine, refined antibodies, small molecules, and repurposing of existing products provides a strong foundation for further and monumental achievements.

Stephen C. Groft, Pharm. D.
Director, Office of Rare Diseases Research
National Center for Advancing Translational Sciences
National Institutes of Health

Steve Groft, who has devoted more than 30 years to rare diseases research and 40 years to public service, retired from the NIH in February.

See more at **www.phrma.org/catalyst/Addressing-Challenges-in-Rare-Disease-Drug-Development-Together#sthash.RYbyQA2h.dpuf**

Clinical Trial Offshoring

by *Roy Zeighami* and *Stephanie Bozarth*

There are an estimated 7,000 rare diseases, of which 80 percent are genetic. Yet during the first 25 years of the Orphan Drug Act only 326 new drugs or therapies for rare diseases were approved by the U.S. Food and Drug Administration (FDA). With approximately 450 new rare disease therapies in the pipeline, most rare diseases have no therapy approved or in the planning stages.

Participation in the early phase clinical trials of new therapies offers hope for patients for whom therapies are not approved. Although several of the MPS diseases (MPS I, MPS II, MPS IVA and MPS VI) have FDA-approved therapies, the remaining do not (MPS IIIA, IIIB, IIIC; MPS IVB; MPS IX, and ML II, II/III and III). In the last several years many phase I/II clinical trials have been conducted outside the United States, "offshored," shutting out participation by U.S. patients and denying them access to experimental treatments.

Recent legislative advocacy has succeeded in passing laws to speed approval of therapies for rare and life-threatening diseases. However, the provisions do not address the epidemic of rare disease clinical trials being offshored outside the United States.

Rare Disease Advocacy: FDASIA

In 2012 the rare disease community collectively advocated Congress for language to be incorporated into the Food and Drug Administration Safety and Innovation Act (FDASIA). That language specifically allows the FDA to base accelerated approval for rare disease therapies on surrogate endpoints, in addition to the standard clinical endpoints. Although accelerated approval had been granted by the FDA for cancer and HIV therapies, it has only been granted once for a rare genetic disease. The National MPS Society, along with other organizations, is following the progress of FDA implementation of the approved language, to ensure it meets the intent of the law. The Society sent action alerts asking for your support throughout this process, and we hope you will continue your support when requested.

What are surrogate endpoints and accelerated approval?

A surrogate endpoint is a biomarker that is used to measure the effect of therapy. An example of a biomarker for MPS diseases are glycosaminoglycans (GAGs). GAG reductions may be detectable immediately while improvement in a six-minute walk test may take months of therapy. Therefore, use of surrogate endpoints enables the FDA to approve therapies faster—accelerated approval—rather than relying only on clinical endpoints that take months to show significant improvement, such as the six-minute walk test or three-minute stair climb.

Why is accelerated approval important?

Using surrogate markers to accelerate approval saves valuable time during the therapy approval process and moves the therapy to market faster. Ultimately this can reduce the costs to industry for approval of therapy and increase the goal of global access. For our children, time is critical as they continue their fight against MPS while waiting for a therapy.

Overview of Clinical Trial Phases

Clinical trials are typically broken into four phases. The goal of phase I is to determine the safety of the therapy; in phase II the effectiveness of the therapy is studied in a small number of patients. In clinical trials for rare diseases, phase I and II are often combined because of the small patient populations. If the results from phase I/II are positive, the clinical trial moves to phase III where safety and effectiveness are studied in a larger population of patients. Phase IV occurs after the FDA has approved the therapy and includes FDA requirements, generally to gather additional information about safety, effectiveness and optimal use.

Decrease of Phase I/II Trials in the United States

In the last several years, many phase I/II clinical trials have been conducted outside the United States, "offshored," shutting out participation by U.S. patients and denying them access to experimental treatments. This has been true for several enzyme replacement

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>> therapies for MPS and other lysosomal storage diseases. Offshoring of early clinical studies delays U.S. patient access to life-saving experimental treatments for as much as two years or longer. For most MPS and related diseases, two years is much too long to wait as these are progressive diseases, and the average life span is around 14 years of age.

The Reason for Offshoring

Safety for all drug development requires testing and toxicology studies. The International Conference on Harmonization (ICH) sets guidelines for safety testing and does allow for flexibility in certain circumstances. The regulatory authorities (e.g., FDA) interprets the guidelines and then applies them to the regulatory framework, as the internal guidelines for drug approval process.

Currently, the FDA adheres to a much stricter interpretation of the ICH guidelines than regulatory authorities in some other countries and requires extensive toxicology studies prior to human studies. This requirement drives up time and cost of research and the development of drugs. For rare diseases, many companies developing therapies are conducting the early clinical trials (phase I/II) in the United Kingdom and Europe so they can move quickly from bench to bedside. This allows them to avoid additional years of safety studies on a known protein with low toxicity probability and also to decrease costs. Over the last decade, science has improved significantly to understand diseases, safety data and the human body, but the FDA has not changed their internal guidelines to reap the benefits of disease knowledge and scientific advancement.

Beyond the Patient Impact

Clinical trial offshoring impacts the U.S. medical community as well. Clinical trials exist to advance science. If U.S. doctors are not conducting these trials then they are not at the forefront of advancing science. This puts our researchers at a disadvantage professionally. It also perpetuates the process of moving trials outside the United States.

Clinical trials support many jobs, from the nurses who coordinate the trials, to the teams that handle regulatory interactions and manage the supply of drug. Those jobs are lost when clinical trials are offshored.

National MPS Society's Legislative Agenda and How You Can Help

As members of the National MPS Society's Legislative Committee, we see clinical trial offshoring as a major detriment to our kids. Although the issues are highly technical, our goal is to get to the heart of the matter and identify what is needed to affect change. However, we can't make change without your help. The Society will continue to send action alerts to you via e-mail. Your participation in these action alerts is critical! It sends the message to your members of Congress that you care. Also, please recruit your family and friends to participate in our action alerts. By forwarding your action alert e-mail, anyone can advocate on your behalf.

We want to hear from you!

Do you want to see certain issues addressed? Do you need help filling out the forms? Drop us a line and let us know.

Stephanie Bozarth, MSW
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Parent of Annabelle (MPS IV)
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NIH Makes Palliative Care More Attainable for Pediatric Patients and Their Families

Conversations Matter campaign helps ensure children with serious illnesses and their families get supportive care

A campaign just launched by the National Institute of Nursing Research (NINR) aims to increase the use of palliative care—comprehensive treatment of the discomfort, symptoms and stress of serious illness—for children with serious illness.

Palliative care can reduce a child's pain, help manage other distressing symptoms, and provide important emotional support to the child and family throughout the course of an illness.

Research has shown that pediatric palliative care services also may increase overall satisfaction with care for patients and their families. Yet, many healthcare providers hesitate to recommend palliative care for their youngest patients, and parents and caregivers are often unaware of its benefits.

"Initiating palliative care conversations is often hard for both providers and families, especially in the pediatric setting," said Dr. Patricia A. Grady, NINR director. "While it may not be an easy conversation, recommending palliative care to patients and families early can improve patient experiences with care. We hope this campaign and its resources will help ensure that palliative care is considered for every child and family navigating a serious illness."

To develop the Palliative Care: Conversations Matter campaign, NINR, a component of the National Institutes of Health, brought together parents and palliative care clinicians, scientists and professionals to give their input and expertise on what they felt was needed in the field. The campaign emphasizes that palliative care works along with other treatments to enhance quality of life for children of any age living with a broad range of serious illnesses. In particular, the campaign strives to break the common association between palliative care and hospice care, stressing that palliative care is appropriate throughout illness, not only at the end of life.

The campaign's evidence-based materials are designed to help providers initiate palliative care conversations with pediatric patients and their families as soon as possible following diagnosis, and to continue these discussions throughout the illness to meet changing needs of the patient and family.

The Palliative Care: Conversations Matter campaign resources include:

- Informational video vignettes, which offer advice to providers about how to start palliative care discussions with patients and family members, and features a mother's perspective on palliative care after her daughter's difficult diagnosis.
- Customizable tear-off pads of patient education sheets, in English and Spanish, which encourage providers to have discussions with patients and their families by providing answers to common questions about palliative care and resources to support conversations.

To learn more about the Palliative Care: Conversations Matter campaign or to download or order campaign materials, visit **www.ninr.nih.gov/conversationsmatter or call 301.496.0207**.

Personal Stories: Speaking Before the FDA Advisory Committee

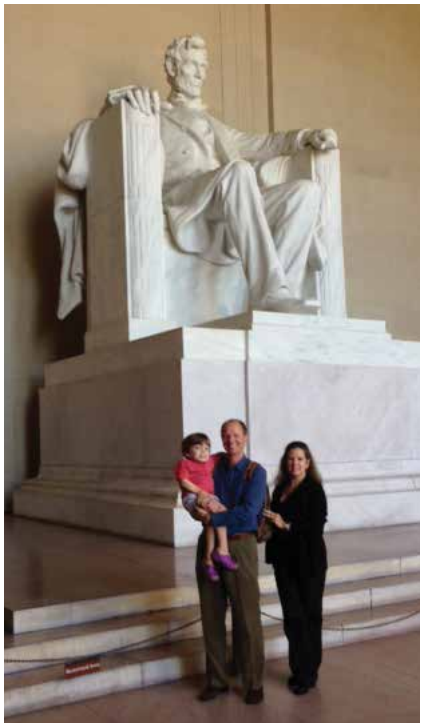
The winter issue of *Courage* 2013 addressed the November meeting of the FDA Advisory Committee in Washington, DC, to consider approving Vimizim™ (elosulfase alfa), the enzyme replacement therapy (ERT) for MPS IVA (Morquio syndrome.) It was a historic day for patients with MPS IVA when the committee voted 19-1 to recommend approval of Vimizim.

Six MPS IV families told their stories to the committee and they were beyond amazing. Their finely tuned, five-minute talks brimmed with heartfelt details about the devastating disease they face daily. We asked the families to share their thoughts about that day and their preparations.

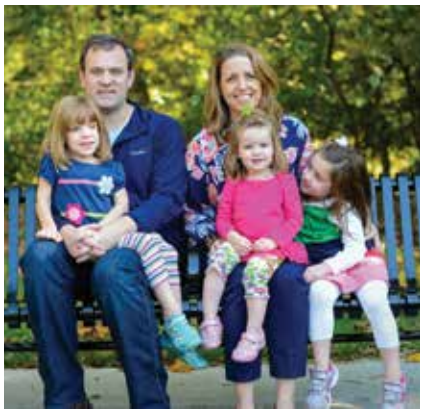
"WE WERE SO GRATEFUL to have the opportunity to attend the FDA Advisory Committee meeting. Living in Hawaii, we have only had a few chances to meet people throughout the MPS community. While this was a very quick trip to the Washington, DC, area, we cherish the experience of meeting everyone there. It was humbling to meet so many amazing MPS patients and families. Everyone from the National MPS Society, the National Organization for Rare Disorders (NORD) and Biomarin have been so kind and generous with support for all of us. We are fortunate to have such committed advocates working on behalf of us and our loved ones affected by MPS. We witnessed the Advisory Committee as they listened, contemplated and questioned Biomarin, weighing the risks and benefits of Vimizim treatment. Kudos to the Biomarin team for their brilliant presentation. There was an overwhelming amount of information for the committee to process during the day, with serious consequences in the balance. It was an impressive collaboration of efforts toward a common goal.

"At the end of the day, we realized we were part of a once-in-a-lifetime experience during a historic day for the Morquio community. We look forward to seeing and hearing from our new friends soon. Special thanks to the National MPS Society, NORD and Biomarin for making it all happen. Your work is inspiring and appreciated!"

Jake (MPS IVA), *Doug and Heidi Kreul*



Jake (MPS IVA), Doug and Heidi Kreul



Annabelle (MPS IVA), Austin, Stephanie, Charlotte and Madeline Bozarth

"ON SEPT. 21, 2011, Annabelle (5 years old at that time) received her first ERT as part of the BioMarin Pharmaceuticals pivotal phase III clinical trial. Since then, we have committed every single week to traveling back and forth to ensure that Annabelle receives her weekly dose of enzyme along with extra lab work, exams, questionnaires and back-to-back daily endpoint testing. Like so many families, we have been totally committed to this trial, and as we began to slowly see Annabelle's stamina and energy improve along with less pain, it was clear—we made the right decision for our daughter. Our sacrifices to participate were well worth the benefit in her quality of life. As parents it is impossible to not be immensely hopeful and slightly biased at wanting to see improvements, but when I took her stroller out of our SUV and placed it in the garage because we didn't need it but only on occasion, I KNEW for a fact Annabelle's improvements were **very** real.

"When I learned the FDA had requested an Advisory Committee hearing to gather more information about the results of the BioMarin ERT trial, I was first in line to testify in the open public hearing. It was critically important, as it was our chance to share how the ERT has significantly improved Annabelle's quality of life. Beyond the six-minute walk test or three-minute stair climb endpoints, I had to share what these improvements meant to Annabelle's everyday life. She is a much different kid today. She has energy that almost mirrors that of my other two unaffected young daughters. She might not run as fast or jump as high, but she keeps up! She is feeling better and able to engage in life as a kid.

"Our historical day at the FDA to testify about ERT was nerve-racking, exciting, emotional, but most of all hopeful for a much different future than what we were told at her diagnosis. I am grateful for BioMarin for investing in research, development and bringing to the bedside the very first treatment for Morquio syndrome. I also am grateful for the opportunity and applaud the FDA for listening to those who matter the most in this process—the patients and families that love them dearly."

Stephanie Bozarth

"WHEN WE WERE CONTACTED by Barbara Wedehase, asking for Sarah to speak to the FDA Advisory Committee, we were excited. Sarah was nervous about this big undertaking as well. The whole family wondered if the voice of one 16-year-old girl would make a difference to this big government agency.

"Sarah decided to consult her beloved creative writing teacher, Brian Earley, to assist her with writing her speech. They had a number of meetings to create a speech that captured her experience with Morquio syndrome as well as her experience with Vimizin. The result was an awesome speech that captured Sarah's spirit and her winning attitude.

"While it was a bit nerve-wracking for Sarah, it was awesome to work with the team to understand the process that was going to occur the next day. We realized this was huge; our daughter was going to help others in a way that we never imagined. Listening to everyone's speech, we understood the true impact of this drug on the lives of others. We were humbled by their stories.

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>> “As Nov. 19 dawned, Sarah was extremely nervous. We boarded the bus and headed to the FDA campus. We were told we had options to leave the hearing if necessary to get a break from the activities. We stayed the entire time. The process was so intense! I have been a nurse for 26 years and I had never witnessed any FDA activity. The whole family was intrigued and hanging on every word. Our daughter Amanda was listening to the webcast since she was at college. We did our best to keep our poker faces but we couldn’t always hide our exasperation at some of the questions.

“After lunch the open public hearing began. Sarah had been assigned the number three spot. We listened intently to the first two speakers and then it was time. Tom, Tommy and I stood behind Sarah (after we helped her to stand on the chair), offering our love and support. The pride we felt at Sarah’s brave story cannot be described. We were nervous when her emotions got the better of her. I was so worried about the clock winding down (each speaker had five minutes maximum to talk). We were thankful that the Advisory Committee allowed the clock to be reset and to hear the rest of Sarah’s story. It was a very emotional experience for all of us. The text messages came flying from near and far from our family and friends who had been listening to the webcast.

“We feel blessed that Sarah was chosen to share her story. We will always remember this experience, the day our daughter made a difference to the MPS Morquio A community.”

Ruthann Van Orden

Tommy, Ruthann, Tom and Sarah (MPS IVA) Van Orden